Request for Reconsideration filed November 30, 2000. The Examiner's acknowledgement thereof is respectfully requested.

REJECTION UNDER 35 U.S.C. 101

The Examiner rejects claims 21, 23 and 25 under 35 U.S.C. §101 for the alleged reason that the claimed invention is not supported by either a specific asserted utility or a well established utility. Applicants respectfully disagree with the Examiner's position.

Claim 25 is directed towards a polypeptide encoded by a nucleic acid construct, which is further defined in features a) to d). Claims 21 and 23 refer to a method for preparing such a polypeptide. Example 2 on page 50 discloses a method for preparing a polypeptide employing kidney cells and also discloses a polypeptide as covered by claim 25, i.e. factor X, which is a zymogen that is activated by cleavage of an inhibiting part of the precursor of Factor X, and that has been engineered to contain a cleavage site for the prostate specific antigen (PSA) protease instead of the natural factor X cleavage site. As described on page 49 of the specification, the PSA which is secreted by prostate carcinoma metastases is able to specifically activate the modified FX, thereby initiating coagulation which leads to interruption of the blood supply to the metastasis, and consequently to necrosis of the metastasis. According to MPEP §2107.01(II)(A), "[a] disclosure that identifies a particular biological activity of a compound and explains how that activity can be utilized in a particular therapeutic application of the compound does contain an assertion of specific utility for the invention." Here, the biological activity identified is the initiation of coagulation, and the therapeutic application utilizing this activity is the deprivation of blood flow to a tumor. Thus, a specific utility has been asserted. The Examiner points out on page 4 of the Office Action that no specific examples of polypeptides are disclosed in the specification for use in the treatment of

other diseases. However, the MPEP clearly states that, "an applicant need only make one credible assertion of specific utility for the claimed invention to satisfy 35 U.S.C. 101 and 35 U.S.C. 112." MPEP §2107.01(I). Therefore, the remaining question in judging utility under 35 U.S.C. 101 is whether the asserted utility is substantially credible.

With respect to the credibility of the asserted utility, Federal Circuit case law directs the USPTO to presume that a statement of utility made by an applicant is true. *See* MPEP §2107.01(III)(A), citing *In re Langer*, 503 F.2d 1380, 1391, 183 USPQ 288, 297 (CCPA 1974); *In re Malachowski*, 530 F.2d 1402, 1404, 189 USPQ 432, 435 (CCPA 1976); *In re Brana*, 51 F.3d 1560, 34 USPQ2d 1436 (Fed. Cir. 1995). To overcome this presumption, Office personnel must establish through evidence that it is more likely than not that one of ordinary skill in the art would doubt the truth of the statement of utility. MPEP §2107.01(III)(A). This is a preponderance of the totality of the evidence standard and rejections under this standard have been upheld in the Federal Circuit only in rare cases, such as when the asserted utility could only be true if it violated a scientific principle, such as the second law of thermodynamics, or was wholly inconsistent with contemporary knowledge in the art. MPEP §2107.01(III)(A)-(B). In an attempt to reach this high standard, the Examiner questions whether it will be possible to obtain an adequate amount of active protease at the target site to cleave the polypeptide of the present invention. As a basis for this inquiry, the Examiner cites several publications that disclose the presence of protease inhibitors in serum like, for example, ACT, which is capable of inactivating secreted PSA outside tumor cells. It is this observation which the Examiner relies upon to cast doubt on the credibility of the asserted utility. However, the Examiner, in fact, acknowledges an important aspect of the present invention, *i.e.*, the polypeptides are not activated everywhere in the body of a patient, which of course would be detrimental to the treated patient, but only at the site of the release of the protease which in this case is the tumor. Hence, the factor X derived polypeptide disclosed in

Example 2 will only be activated in the tumor. Citing the publication of Denmeade, SR et al (1997), however, the Examiner attempts to support this rejection by claiming that Denmeade et al. showed that even the PSA secreted at the tumor site forms complexes with ACT and becomes inactivated. Yet, as the Examiner also acknowledges, the released protease (PSA in this case) is initially active and only subsequently becomes inactivated. Denmeade et al suggest that this short window of activity of the protease, PSA, in the vicinity of the tumor can be used for the selective activation of peptide-coupled prodrugs to treat metastatic prostate cancer, *i.e.*, they propose exactly the type of utility for protease activatable polypeptides that is asserted in the present application. See last sentence of the abstract:

" It should be possible to use HSSKLQ peptide as a carrier to target peptide-coupled-pro-drugs for selective activation within sites of PSA-secreting, metastatic prostate cancer cells and not within the blood or other non prostatic normal tissues- " (Emphasis added)

Thus, the very publications cited by the Examiner to cast doubt on the utility of the polypeptides of the present invention in fact substantiate the credibility of the asserted utility.

The Examiner also asserts on page 5 that it is not clear what compound is the precursor of factor X. However, as is evident from, for example, the Gene Bank entry for factor X submitted as EXHIBIT A the factor X precursor has been known since 1986 (see, for example, Gilgenkrantz, S. (1986) Ann. Genet. 29: 32-35 or Leytus, S.P. et al. (1986) Biochemistry 25: 5098-5102), from which it is also known that factor X is initially expressed as a precursor that is converted to a mature two-chain form by the exision of the tripeptide RKR. Thus, the precursor of factor X as well as the natural cleavage site of that precursor for activating the naturally occurring factor X were both

well known in the art. Example 1 describes the generation of a nucleic acid construct encoding a factor X that is cleavable by PSA and also makes reference to Figure 3 (see lines 33-35 on page 49).

This Figure shows that the only change introduced into the naturally occurring factor X is the replacement of Arg at amino acid position 195 with Tyr, thereby converting the natural cleavage site of factor X into a cleavage site that is specifically recognized by PSA. The Examiner argues on page 5 that, "[i]t is not clear whether the presence of the precursor, which is presumably a large molecule, and is bound to the PSA-specific cleavage site, a small peptide, would interfere with the activity of PSA in cleaving the PSA-specific cleavage site." However, the examiner points to no evidence that suggests there would be such interference. Accordingly, the examiner has not articulated sound reasons why a person of ordinary skill in the art would conclude that it is more likely than not that the asserted utility is not credible. Further, as stated above, Denmeade et al contemplated the use of peptide coupled prodrugs that could be cleaved by PSA in the vicinity of metastatic prostate cancer cells. Consequently there is direct evidence to suggest that one of skill in the art (Denmeade et al) would find it credible that the disclosed modified factor X can be cleaved and activated by the active PSA that is present in the vicinity of a tumor. The specification also provides data which shows, in vitro, that transduced HEK 293 cells express mutated FX which, in the added presence of PSA, counterbalances the coagulation defect of FX-deficient plasma, thereby suggesting that PSA is, in fact, able to cleave the modified factor X cleavage site. See Example 2, pages 50-51.

The Examiner questions, even if there is an adequate amount of activated factor X at the tumor site to induce coagulation, whether there would be sufficient coagulation to inhibit growth of new blood vessels induced by prostate cancer metastasis. In the Examiner's hypothetical, the precursor of factor X has already been cleaved at the tumor

site creating an amount of activated factor X sufficient to cause blood coagulation. The inquiry into utility need go no further, because the initiation of coagulation at the tumor site is a useful result. As stated above, this coagulation is the identified biological effect, and it has a reasonable correlation with the asserted utility of depriving the tumor of blood flow. "The applicant does not have to prove that a correlation exists between a particular activity and an asserted therapeutic use of a compound as a matter of statistical certainty, nor does he or she have to provide actual evidence of success in treating humans where such a utility is asserted. Instead, as the courts have repeatedly held, all that is required is a reasonable correlation between the activity and the asserted use." MPEP §2107.02(I). Thus, it is unnecessary for the applicants to prove that there would be sufficient coagulation to inhibit growth of new blood vessels in the tumor; there is a reasonable correlation between localized coagulation and the inhibition of angiogenesis.

The Examiner questions whether the claimed polypeptide would be effective in treating cancer, in view of the lack of guidance on dosage and schedule of treatment, as well as unpredictability of cancer therapies. As stated in the specification on page 45, the effective amount of a preparation can be "determined by the skilled artisan considering variables well known in the art such as the nature of the applicable disease or condition, the nature of the patient, mammal or cells being treated and the method of administration." Specific disclosure of dosage and schedule of treatment would require the completion of phase-III clinical trials. This would also be the only way to overcome the alleged unpredictability of cancer therapies. This burden of disclosure is explicitly denied in the MPEP §2107.02(IV) which quotes *Ex parte Balzarini*, 21 USPQ2d 1892 (Bd. Pat. App. & Inter. 1991), "human clinical data is not required to demonstrate the utility of the claimed invention, even though those skilled in the art might not accept other evidence to establish the efficacy of the claimed therapeutic compositions and the operativeness of the claimed methods of treating humans."

The examiner again points out that the same alleged defects apply to other contemplated constructs of the invention for the treatment of other diseases. However, as stated above, "an applicant need only make one credible assertion of specific utility for the claimed invention to satisfy 35 U.S.C. 101 and 35 U.S.C. 112." MPEP §2107.01(I).

The Examiner also suggests that even if the invention were to work as claimed, it would lack utility if the target cell had an alternative means of survival. Applicant respectfully disagrees with this assertion. Hypothetically, if the claimed compound restricted blood flow to a tumor, and the tumor had an alternative means of survival that could be stopped by a second, non-claimed compound; both compounds would have utility even though neither compound on its own could destroy the tumor. The claimed compound would be useful in the treatment of a tumor in conjunction with the non-claimed compound.

The Examiner lists a series of factors that could potentially have an adverse effect on successful therapy, including: biological stability, half-life, clearance from the blood, degradation, immunological activation, inability to penetrate tissues or cells, absorption, and insufficient circulation in the target area to carry the formulation in appropriate concentrations. The Examiner supports the rejection of the claims on the basis that the specification offers insufficient guidance on these issues, provides no working examples, and offers no evidence to allow one skilled in the art to predict the efficacy of the claimed methods with a reasonable expectation of success. However, this is not the applicant's burden. Once the applicant has asserted a specific utility, it is presumed valid and the burden is on the Examiner to rebut that presumption with specific evidence. The Examiner has merely listed these factors and offered nothing to suggest that any of them would have a significant adverse effect on the therapies contemplated by the claimed invention.

In addition, the Examiner asserts that it is not clear how cells, which are *ex vivo* transfected with the claimed nucleic acid construct, could be used for treating numerous diseases. However, *ex vivo* transfected cells are only used for the *ex vivo* production of the polypeptides of the present invention, which then in turn can be, for example, applied to a patient. Therefore, the rejection based on the lack of guidance on the necessary dosage and schedule of treatment using cells transfected with the claimed nucleic acid is moot since the use of *ex vivo* transfected cells is not claimed.

In summary, the specification asserts a specific utility for the claimed polypeptide which is presumed credible and further shown to be credible in view of the teaching of the specification itself, in view of the publications cited by the Examiner, and in view of further evidence submitted as EXHIBIT A. This utility asserted, the burden is on the Examiner to rebut the presumption and evidence of credibility through specific evidence showing that one of skill in the art would doubt the credibility of the asserted utility. Because the examiner has not met this burden, Applicant respectfully requests that the rejection of claims 21, 23 and 25 under 35 U.S.C. 101 be withdrawn.

REJECTION UNDER 35 U.S.C. 112, FIRST PARAGRAPH, ENABLEMENT

The Examiner rejects claims 21, 23, and 25 under 35 U.S.C. 112, first paragraph, as lacking enablement, for the reasons of record in paper No. 8. The reasons set forth in paper No. 8 are the same as those listed under the section 101 argument in the pending Office Action. Accordingly, with the withdrawal of the rejection of claims 21, 23 and 25 under section 101, Applicants respectfully request the withdrawal of the rejection of those claims under section 112, first paragraph for lack of enablement.

REJECTION UNDER 35 U.S.C. 112, FIRST PARAGRAPH, SCOPE

The Examiner rejects claims 21, 23 and 25 under 35 U.S.C. 112, first paragraph, on the assertion that the scope of the claims is broader than the specification supports. Specifically, the Examiner suggests that the specification does not support polypeptide constructs comprising an amino acid sequence cleavable by any protease, which could be released by any mammalian cell, i.e. that the polypeptides are already cleaved in the serum. The assertion that the polypeptides of the present invention will be inactivated by a number of proteases that are active in serum is a surprising argument given the reasoning of the Examiner on page 4 of the Office Action, where the Examiner asserted that "it is well known in the art that most PSA in the serum is inactive, by complexing with a protease inhibitor, ACT," and further argued, "this type of protease/protease inhibitor complexation in serum...is well known in the art and could apply as well to the claimed proteases other than PSA, such as cathepsin, plasminogen activator, etc." Thus, in view of the very arguments and evidence provided by the Examiner with respect to utility, the alleged ubiquitous activation of the polypeptides of the present invention appears highly unlikely. Rather, as is evident from Denmeade et al, the polypeptides will only be cleaved and activated at the site of the release of the respective protease, in the short time before the protease is inactivated by complexation with an inhibitor. This cleavage is effected by recognition of the respective part structure c) of the polypeptide of the present invention. Accordingly, it is respectfully requested that the rejection under 35 U.S.C. 112, first paragraph, of claims 21, 23 and 25 be withdrawn.

For the aforementioned reasons, Applicants request the withdrawal of all pending rejections of claims 21, 23 and 25. Applicants believe that the foregoing arguments place this application in condition for allowance, and respectfully request rejoinder of claim 19

with the other claims of group III in accordance with MPEP §821.4 and U.S. Patent and Trademark Office Procedure.

Respectfully submitted,

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